Extracolonic Findings on CT Colonography Increases Yield of Colorectal Cancer Screening

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OBJECTIVE. The purpose of this study is to evaluate the impact of extracolonic findings when screening is undertaken by CT colonography (CTC).

MATERIALS AND METHODS. We performed a retrospective cohort study of patients completing a screening CTC from August 2003 to June 2006 at Walter Reed Army Medical Center. Extracolonic findings were categorized using a CTC reporting and data system that classifies findings as highly significant, likely significant, and insignificant. All final diagnoses, surgeries, malignancies, and costs of diagnostic radiology procedures were calculated for each category.

RESULTS. Of 2,277 patients (mean ± SD age, 59 ± 11 years; 60% white; 56% male) undergoing CTC, extracolonic findings were identified in 1,037 (46%) patients, with 787 (34.5%) insignificant and 240 (11.0%) significant findings. Evaluation of significant findings generated 280 radiology procedures and 19 surgeries over a mean follow-up time of 19 ± 10 months. The total cost of the radiology studies was $113,179; the studies added approximately $50 extra per patient. Seven high-risk lesions were identified (six extracolonic malignancies and one large aortic aneurysm) in patients with significant findings. CTC also identified six intracolonic malignancies and three adenomas with high-grade dysplasia. When considering extracolonic findings, CTC increased the odds of identifying high-risk lesions by 78% (nine intracolonic lesions vs 16 intracolonic plus extracolonic lesions; $p = 0.0156$). Of the 16 intracolonic and extracolonic high-risk lesions, 11 (69%) underwent curative resection, and 5 of 11 (44.4%) were extracolonic.

CONCLUSION. CTC increased the odds of identifying high-risk lesions by 78%. CTC should be considered as an alternative to optical colonoscopy for colorectal cancer screening or as a onetime procedure to identify significant treatable intracolonic and extracolonic lesions.

Keywords: colon cancer, CT colonography, extracolonic findings, high-risk lesions, screening

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CT colonography (CTC) is an emerging noninvasive rapid imaging technique developed for colorectal cancer (CRC) screening [1, 2]. In some centers, it is being used as an alternative to optical colonoscopy with comparable sensitivities and specificities [3, 4]. CTC is less invasive than optical colonoscopy and may improve patient adherence and CRC screening.

In addition to intracolonic findings, CTC examines the entire abdomen and pelvis similarly to a CT scan [5, 6]. These extracolonic findings categorized as significant or insignificant, with 10–23% of all patients having significant findings requiring further radiologic evaluation [5, 7–11]. The ability of CTC to identify significant extracolonic lesions at an early treatable stage may increase the yield of CRC screening, thus enhancing CTC as a major screening technique.

The goal of this study was to evaluate the impact of extracolonic findings when screening is undertaken by CTC. “We quantified impact by detecting significant new extracolonic lesions by tracking radiology costs generated, surgical procedures performed, and new malignancies identified.”

Materials and Methods

Study Group

This was a retrospective review of all CTC studies performed at the Walter Reed Army Medical Center from August 19, 2003, to June 19, 2006. At our institution, the primary techniques for screening include optical colonoscopy and CTC. CTC is used predominantly as a screening tool (> 99%) and secondarily for incomplete colonoscopies. All patients are military health care beneficiaries and must be referred by their primary care provider or from the gastroenterology clinics in the Washington, DC; northern Virginia; and Maryland area. Our virtual colonoscopy program screens all patients to ensure that the indication for CTC is appropriate. Patients with hematochezia, a history

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of CRC or polyposis syndromes, or any other contraindications to CTC would generally be excluded. All demographic information (age, sex, and race) was obtained from data collected by the technician at the time of CTC. Demographics, location, and type of extracolonic finding were entered into the CTC database and secured on a password-protected computer. The protocol was approved by the Walter Reed Army Investigational Review Board (work unit 07–14031EX).

CTC Technique

All patients underwent standard bowel preparation, which included either polyethylene glycol (4 L) or a split dose of 45 mL of sodium phosphate the day before the procedure in addition to a single dose of 2% barium sulfate (250 mL) and diatrizoate sodium (60 mL) to tag the stool and colonic fluid, respectively. On the day of the procedure, the colon was inflated using an automated low-pressure carbon dioxide delivery system (PROTOCO$_2$L, E-Z-EM) with CT scout scans obtained before each study to ensure full colonic distention and an adequate field of view.

Examinations were performed using MDCT scanners (8-, 16-, or 64-MDCT scanner; LightSpeed, GE Healthcare). CT scans were performed using a slice thickness of 1.25 mm, equivalent pitch of 1.5, 1 mm reconstruction interval, 100 mAs, 120 kVp, 512 × 512 matrix, and a single 5–20 second breath-hold. Both supine and prone acquisitions were obtained for all patients.

The image data were networked to a workstation using 3D colon software (V3D Colon, Viatronix). CTC-trained experienced radiologists read each study at the time of the examination, and a CTC report was created. All fourteen radiologists who routinely read CTC scans during this period had been trained at Walter Reed Army Medical Center to read CTC scans in a week-long course that required reading scans for 52 pathology-proven cases of CTC along with an oral examination. All CTC scans showing significant lesions were then reviewed by a seasoned CTC radiologist who had read more than 5,000 CTC scans.

CTC Reporting and Data System

In 2005, the Working Group on Virtual Colonoscopy developed a CTC reporting and data system as a way to streamline the classification of both intracolonic and extracolonic findings [12]. The CTC reporting and data system classification provides radiologists with a consistent method to communicate findings, both intracolonic and extracolonic, to providers and patients. They also provide clear recommendations regarding radiologic or clinical follow-up. Standardized reporting can better assist patients and referring physicians in making management decisions on the basis of CTC results [12].

Intracolonic Findings

The goal of screening CTC is to identify intracolonic premalignant lesions in a noninvasive manner. In our institution, the criteria for a positive CTC scan is a polyp 8 mm or larger. Patients with polyps 6–7 mm are recommended to have surveillance CTC at 1 year. Patients with polyps of 8 mm or larger are recommended to undergo a colonoscopy with polypectomy. Polyps are exam-

TABLE 1: CT Colonography Reporting and Data System: Radiologic Method of Categorizing Extracolonic Findings According to Clinical Significance

Score	Description	Examples
E0	Limited examination: compromised by artifact; evaluation of soft tissues is severely limited	Not applicable
E1	Normal examination or anatomic variant: no extracolonic abnormalities visible	Retroaortic left renal vein
E2	Clinically unimportant finding: no workup indicated	Simple renal cyst; gallstones; hiatal hernia
E3	Likely unimportant finding, incompletely characterized: workup may be indicated	Complex renal cyst; lung nodule
E4	Potentially important finding: communicate to referring physician as per accepted practice guidelines	Ovarian mass; kidney mass; abdominal aortic aneurysm (5 cm); lymphadenopathy

Note—Adapted from [12].

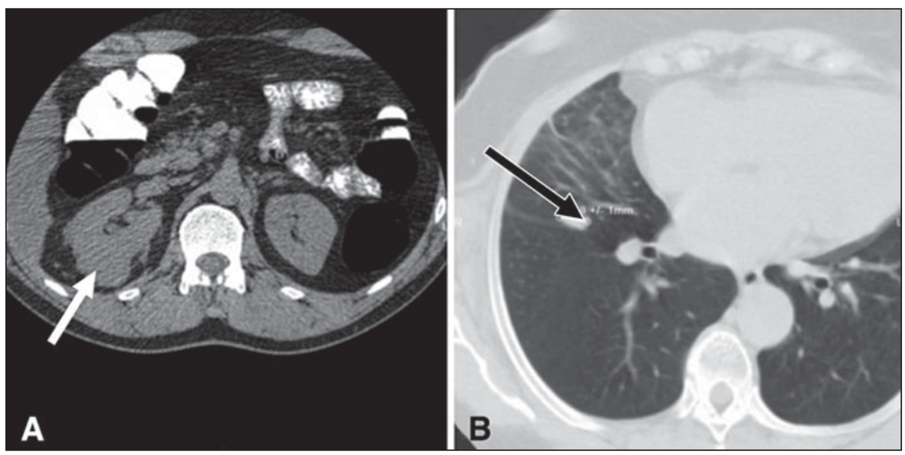

Fig. 1—Examples of extracolonic findings that ultimately represented malignancy.
A, Image shows 5.5 cm partially exophytic mass (*arrow*) arising from lower pole of the right kidney that was eventually diagnosed as stage II renal cell cancer.
B, Image shows lower right lung nodule (*arrow*) that was resected and histologically confirmed as stage I moderately differentiated adenocarcinoma.

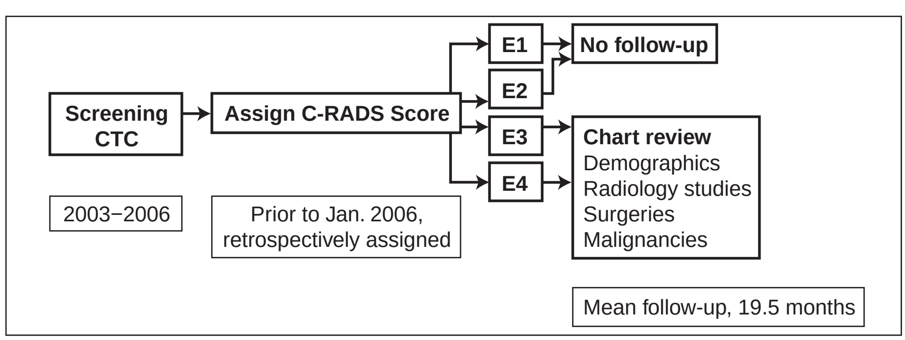

Fig. 2—Retrospective chart review design. C-RADS = CT colonography reporting and data system, CTC = CT colonography.

ined by the pathologist and surveillance recommendations are based on the size and histologic analysis of polyps. In this study, we define an intracolonic high-risk lesion to be an adenoma with high-grade dysplasia or adenocarcinoma.

The CTC reporting and data system classifies these colonic lesions in a systematic way. C0 signifies an inadequate study. C1 describes a normal colon, which means no polyps 6 mm or larger detected. C2 describes intermediate sized polyps (6–7 mm) fewer than three in number that will require CTC surveillance at 1 year or a colonoscopy if chosen. C3 depicts an advanced number of polyps (more than three, 6–9 mm) or larger polyp (≥ 8 mm) that requires a colonoscopy with polypectomy. C4 simply describes a colonic mass that is likely malignant and requires urgent medical and surgical evaluation. According to this categorization system, patients with C2 lesions will undergo a follow-up CTC at 1 year, or colonoscopy if desired, whereas patients with C3 and C4 lesions will only be offered colonoscopy for polypectomy.

Extracolonic Findings

Extracolonic findings are not the primary goal of CTC, but radiologists are responsible for evaluating both intracolonic and extracolonic findings. The focus of the present study was to explore the impact of extracolonic findings on patients undergoing screening CTC. Any patient with an extracolonic finding, whether significant or insignificant, was entered into our database. Our study used a novel categorization system, a CTC reporting and data system [12], to help classify significant versus insignificant extracolonic lesions.

The CTC reporting and data system divides extracolonic findings into four distinct categories (Table 1). E1 describes a normal examination or anatomic variants. E2 describes clinically insignificant findings requiring no further follow-up, such as simple renal or hepatic cysts, uncomplicated gallstones, and kidney stones. E3 describes likely insignificant findings not completely characterized by CTC requiring a nonurgent workup; examples include small pulmonary nodules and complex renal or ovarian cysts. E4 defines significant findings that are potentially dangerous and require an expedited workup with at least one other radiology study. Examples of E4 findings are potential malignancies or large abdominal aortic aneurysms [12] (Fig. 1). According to this classification, only extracolonic findings assigned to E3 or E4 by the CTC reporting and data system would be recommended for further radiologic and medical follow-up. For our study, a high-risk extracolonic finding would be a lesion that went on to be a malignancy on the basis of pathologic findings or a large abdominal aortic aneurysm (≥ 5 cm) confirmed in the operating room.

Assignment of CTC Reporting and Data System

Because the CTC reporting and data system was not implemented until January 1, 2006, all CTC scans performed between July 2003 and January 1, 2006, were retrieved, and a board-certified radiologist experienced with the CTC reporting and data system reviewed and assigned each CTC report a score based on the CTC reporting and data system. CTC studies performed after January 1, 2006, were routinely given a CTC reporting and data system score (E1, E2, E3, or E4). For patients with multiple extracolonic findings, the CTC reporting and data

TABLE 2: Medicare Reimbursement Rates at Walter Reed Army Medical Center for 2007

Examination	CPT Code	Price ($US)
CT chest, without contrast material	71250	349.81
CT chest, with contrast material	71260	414.84
CT chest, with and without contrast material	71270	511.31
CT abdomen, without contrast material	74150	337.84
CT abdomen, with contrast material	74160	417.06
CT abdomen, with and without contrast material	74170	522.46
CT pelvis, without contrast material	72192	341.74
CT pelvis, with contrast material	72193	397.08
CT pelvis, with and without contrast material	72194	490.14
MRI abdomen, without contrast material	74181	625.24
MRI abdomen, with contrast material	74182	776.83
MRI spine	72149	765.66
MRI pelvis	72196	755.49
Ultrasound pelvis	76856	123.53
Ultrasound examination, abdomen, complete	76700	105.47
Ultrasound retroperitoneal (e.g., renal, kidney)	76770	143.43
Tumor imaging PET, whole body	78813	1,150.00
Bone or joint imaging, whole body	78306	269.21
Endoscopic ultrasound examination, esophageal	43237	239.59
Esophagogastroduodenoscopy, upper endoscopy	43235	144.62
Bronchoscopy	31622	153.90
Mammogram, screening	77057	70.60
X-ray abdomen	74000	23.89
Upper gastrointestinal series	74246	126.85
X-ray pelvis	72170	33.56
X-ray spine	72020	28.03

Note—CPT = Current Procedural Terminology.

TABLE 3: Demographic Data on All Patients With Extracolonic Findings Categorized by CT Colonography Reporting and Data System Score

Demographic Characteristic	All Patients	CT Colonography Reporting and Data System Score			p
		E2	E3	E4	
Age, y, mean ± SD	61 ± 11	61 ± 11	61 ± 11	63 ± 13	0.549
Male (% of patients)	53	54	48	53	0.306
Race (% of patients)					0.136
White	61	63	54	76	
African American	24	23	31	21	
Hispanic or Asian	15	14	15	3	

system score was based on the most significant extracolonic finding. For example, a patient with both E4 and E2 findings would be assigned an E4 CTC reporting and data system score.

Follow-Up of CTC Reporting and Data System Findings

The majority of patients enrolled in our health care system received their entire care in military treatment facilities; however, patients were allowed to seek civilian health care if desired. In this cohort, most patients with new E3-classified (85.6% [167/195]) and new E4-classified (91.4% [32/35]) extracolonic lesions and all patients with significant intracolonic lesions received follow-up evaluations at Walter Reed Army Medical Center or surrounding military treatment facilities. These results were stored in military-wide computer data systems through which all radiologic, histologic, and clinical diagnostic studies could be accessed. Prior existing extracolonic findings and their evaluations were not repeated and included in this study. All follow-up radiologic and surgical procedures were followed over a time interval of 6 months to 4 years (mean follow-up time, 19.5 ± 10 months). The type, number, and results of these examinations were tabulated, including the final diagnosis, surgeries performed, and cancers identified during the evaluation (Fig. 2).

Medical Costs

The total and per-patient cost of the follow-up radiology tests performed to work up patients with significant extracolonic findings (E3 or E4) were calculated using 2007 Medicare reimbursement rates (Table 2). Per-patient cost was calculated by dividing the total cost of radiology or diagnostic studies by the number of patients who underwent a screening CTC scan (n = 2,277). Radiology costs included all radiology studies generated from the workup of an extracolonic finding. We would include the same study up to a maximum of three times; for example, three CT scans of the chest were included in the evaluation of a pulmonary nodule. Surgical procedures were not included in the rudimentary cost analysis. Total cost was based on an 86.5% follow-up rate. We extrapolated the total cost calculations to estimate the total cost and per-patient cost for a 100% follow-up.

Statistical Analysis

Continuous data are expressed as mean ± SD. Categorical data are expressed as ratios and percentages. Differences in patient age between the three CTC reporting and data system scores (E2, E3, and E4) were compared using one-way analysis of variance. Sex and race differences between CTC reporting and data system scores were analyzed with Fisher's exact test. Fisher's exact test was used to compare the proportion of patients with significant lesions or malignancies or who underwent surgery between the CTC reporting and data system groups. McNemar's test was used to compare the number of significant colonic findings versus the total number of overall findings (colonic plus extracolonic). A probability of 0.05 or less was considered to be statistically significant.

Results

Of 2,277 patients undergoing screening CTC (mean age, 59 ± 11 years; 60% white; 56% male), extracolonic findings were identified in 1,037 (46%) patients, with 787 (34.6%) insignificant and 240 (11.0%) significant findings; 54.5% (1,240) of the 2,277 patients had no extracolonic findings (E1), whereas 46% (1,037) had at least one extracolonic finding. Patients with extracolonic findings were classified as follows: E2, 787 patients (34.6%); E3, 211 patients (9.3%); and E4, 39 patients (1.7%) (Fig. 3). Demographic characteristics of patients with extracolonic findings included a mean age of 61.4 ± 11 years old, 53% male, and 61% white. There were no significant demographic differences in the mean age, sex, or race of patients among the different CTC reporting and data system scores (Table 3).

The findings for patients in the E2 group (n = 787) were considered clinically unimportant, 80% of which were renal cysts, nephrolithiasis, hiatal hernias, or benign liver cysts. The majority of findings for patients in the E3 group (n = 211) were pulmonary nodules larger than 5 mm and complex renal and ovarian cysts. New findings were noted in 92.4% (195/211) of patients in the E3 group; 85.6% (167/195) of those patients were followed up in the military health care system (Table 4). E4 lesions were noted in 1.7% (n = 39) of the entire population. Of these findings, 89.7% (35/39) were new findings, and 91.4% (32/35) of these patients were followed up in the military health care system. The most common E4 finding was a kidney mass, which made up 41% (16/39) of E4 findings (Table 5).

According to the CTC reporting and data system recommendations, patients in the E2 group required no further workup and therefore were not assessed in this study. Patients with follow-up for E3 findings (n = 167) generated 158 CT scans, 47 ultrasound scans, five PET scans, nine MRI scans, and 14 other studies. These studies generated a total radiology cost of $87,911. The evaluation of the 32 patients with follow-up for E4 findings generated 24 CT scans, 10 ultrasound scans, five PET scans, four MRI scans, one echocardiogram, one upper endoscopy, one endoscopic

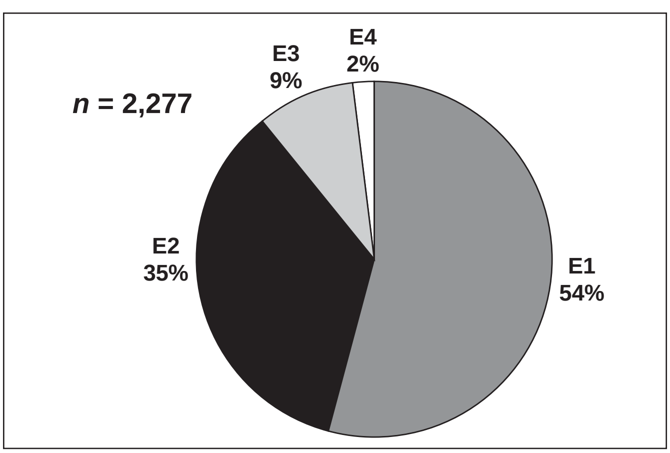

Fig. 3—Extracolonic findings by CT colonography reporting and data system category.

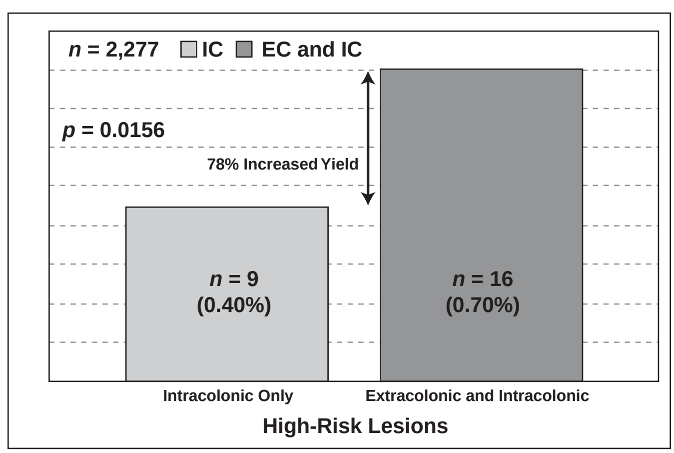

Fig 4—Analysis of both extracolonic and intracolonic lesions, in addition to intracolonic lesions alone, as part of CT colonography evaluation increased yield of identifying high-risk lesions by 78% (n = 9 vs 16; p = 0.0156).

TABLE 4: All E3 Findings Categorized by Organ System

Findings	No. of Patients	New	Follow-Up	Radiology Studies	Surgeries	Final Diagnosis	Approximate Radiology Costs ($US)
Lung: Pulmonary nodules, scars, opacity, plaques, atelectasis, infiltrate, cysts and increased vasculature	71	65	57	89 Lung CT scans, 3 PET scans, 2 chest radiographs	1 Lobectomy	One stage Ia lung adenocarcinoma, 41 pulmonary nodules, 5 granulomas, 3 *Mycobacterium avium intracellulare*, 1 pleural scarring, 1 airspace disease, 1 bronchiectasis, 1 pleural fibrosis, 1 COPD, 1 postinflammatory process, 1 pulmonary fibrosis, 1 normal	40,419
Kidney: Complex renal cysts, renal lesions/densities, polycystic kidney disease, prominent renal pelvis	60	57	45	23 Renal ultrasounds, 34 CT scans of abdomen, 3 MRIs of abdomen, 1 PET	Renal biopsy, radiofrequency ablation	36 Renal cysts, 1 fibroadipose tissue, 1 hydronephrosis, 2 nephrolithiasis, 1 lump kidney, 1 stable renal density, 1 pelvocalictasis, 2 normal	20,959
Liver: Complex liver cyst, liver lesions, hypodensities	16	15	12	2 Liver ultrasounds, 12 liver CT scans	None	6 Liver cysts, 1 fatty liver, 4 hemangiomas, 1 metastatic colon cancer	5,216
Genitourinary: Bladder wall thickening, complex ovarian cysts, bladder herniation, enlarged prostate, endometrial thickening, adenexal lesion, soft tissue pelvic mass, enlarged uterus	20	20	19	19 Pelvic ultrasounds, 3 CT scans of abdomen and pelvis	Bilateral oopherectomy, left oopherectomy, endometrial biopsy	11 Ovarian cysts, 1 fibroid, 1 benign thickened endometrium, 6 normal	4,789
Gastrointestinal: Stomach wall thickening, appendiceal stump, malrotation, hyperdense gallbladder, irregular gastroesophageal junction, small bowel polyp, filling defect in stomach, atrophic pancreas, pancreatic cyst, bilateral inguinal hernias	10	10	10	4 Upper gastrointestinal series, 5 CT scans of abdomen, 1 upper endoscopy	Bilateral inguinal hernia repairs, malrotation correction	1 Mucocele, 1 splenule, 1 pseudocyst, 1 malrotation, 1 bilateral inguinal hernia, 5 normal	2,737
Skeletal: Osteoblastic lesion, osteolytic lesions, osteoporosis, sclerotic lesions, low attenuation lesions, fluid collection right hip, osteoporosis	13	11	10	5 Bone scans, 2 MRIs of spine, pelvis radiograph	None	1 Benign bone island, 1 sacroileitis, 1 hemangioma, 1 benign fluid collection, 3 degenerative disk disease, 1 subchondral cyst, 2 normal	2,911
Adrenal: Adrenal lesion	8	8	7	7 Adrenal CT scans, 4 MRIs of abdomen, 1 PET, 1 ultrasound of abdomen	None	6 Adrenal adenomas, 1 normal	7,282
Vascular: Splenic, abdominal, iliac artery aneurysms	7	6	5	5 CT scans of abdomen, 2 abdominal ultrasounds, 1 CT scan of pelvis	Abdominal aortic aneurysm repair	4 Aneurysms, 1 normal	2,693
Lymphaednopathy: Iliac, perioaortic, mesenteric adenopathy	3	1	0	None	None	No follow-up	0
Other: Mesenteric panniculitis, seroma, bilateral breast nodules	3	2	2	2 CT scans of abdomen, mammogram	None	1 Benign breast density, 1 mesenteric panniculitis	905
Total	211	195	167	158 CT scans, 47 ultrasounds, 9 MRIs, 5 PET scans, 5 bone scans, 4 upper gastrointestinal series, 3 radiographs, 1 upper endoscopy, 1 mammogram	7 Surgeries	1 Cancer	87,911

TABLE 5: All E4 Findings Categorized by Organ System

Findings	New	Follow-Up	Studies	Surgeries	Final Diagnosis	Radiology Costs ($US)
Kidney						
Kidney mass (5.5 cm)	Yes	Yes	Kidney CT scan	Right nephrectomy	Renal cell carcinoma (stage II)	417.06
Kidney mass (2 cm)	Yes	Yes	Renal ultrasound	None	Bosniak II cyst	143.43
Small exophytic projection from left kidney	Yes	Yes	Kidney CT scan, ultrasound of kidney, MRI of kidney	None	Complex renal cyst	1,337.32
Abnormal attenuation of inferior pole of left and right kidney	Yes	Yes	CT scan of kidney, radiograph of kidney, ureter, and bladder	None	Renal cyst	440.95
Left renal mass (8 cm)	Yes	Yes	Adrenal MRI, PET scan	None	Adrenal adenoma	1,926.83
Hyperattenuating mass (1 cm) left kidney	Yes	Yes	CT scan of kidney	None	Papillary necrosis	417.06
Left kidney mass	Yes	Yes	CT scan of kidney, CT scan of abdomen and pelvis	None	Bosniak III cyst	1,231.20
Right kidney mass (4 × 3 cm)	Yes	Yes	CT scan of kidney	None	Simple kidney cyst	417.06
Mass in right kidney (1 cm)	Yes	Yes	Kidney ultrasound	None	Angiomyolipoma	143.43
Solid mass right kidney	Yes	Yes	Kidney CT scan	Right nephrectomy	Renal cell carcinoma (stage I)	417.06
Left exophytic kidney lesion (2 × 6 cm)	Yes	No	None	None	No finding	0.00
Lesion (1.8 cm) adjacent to right renal cyst (7.5 cm)	Yes	Yes	Renal ultrasound, 2 CT scans of kidney	None	Hyperdense renal cyst	977.55
Suspicious kidney mass	Yes	Yes	CT scan of kidney	Nephrectomy	Renal cell carcinoma (stage I)	417.06
Low attenuation masses in kidneys	Yes	Yes	2 CT scans of chest, abdomen, and pelvis	None	Bilateral renal cysts	2,457.96
Bilateral renal masses	Yes	Yes	CT scan of abdomen and pelvis	None	Bilateral renal cysts	814.04
Lobulated mass (3 × 6 cm) superior to kidney	Yes	Yes	CT scan of kidney	None	Lump kidney in midline of abdomen in pelvis	417.06
Gynecology						
Large pelvic mass	Yes	Yes	Pelvic ultrasound	None	Uterine fibroids	123.53
Right ovarian mass (7 × 5.5 cm)	Yes	Yes	Pelvic ultrasound	Right oopherectomy	Complex ovarian cyst	123.53
Left ovarian mass (8 × 10 cm)	Yes	Yes	Pelvic ultrasound	Left oopherectomy	Benign hemorrhagic cyst	123.53
Right adnexal cystic abnormality (6 cm)	Yes	Yes	Pelvic ultrasound	Bisalpingoopherectomy	Fibroadenoma	123.53
Pelvic soft tissue mass (3 × 2 cm)	Yes	Yes	Pelvic ultrasound	Left oopherectomy	Endometrioma	123.53
Bilateral adenexal masses	Yes	Yes	Pelvic ultrasound	Bisalpingoopherectomy	Benign ovarian cysts	123.53
Bilateral ovarian cystic masses	Yes	Yes	Renal CT scan, pelvic ultrasound	Bilateral oopherectomy	Benign ovarian cysts	540.59
Lung						
Lung mass (2 cm)	Yes	Yes	CT scan of chest	None	Calcified granuloma	414.84
Lung mass left lower lobe, bony lesion (2 cm)	Yes	Yes	2 CT scans of chest, PET scan, bone scan, bronchoscopy, MRI spine	None	Benign pulmonary nodule, benign enchondroma	3,294.20
Lower lung lesions suspicious for neoplasm	Yes	Yes	CT chest, PET scan	None	Recurrent bronchoalveolar carcinoma in left lung	1,564.84
Mass in left lower lobe (1.8 cm)	No	No	None	None	No finding	0.00
Right lower lobe mass (4 × 5 cm)	Yes	No	None	None	No finding	0.00

(Table continues on next page)

TABLE 5: All E4 Findings Categorized by Organ System (continued)

Findings	New	Follow-Up	Studies	Surgeries	Final Diagnosis	Radiology Costs ($US)
Lymphadenopathy						
Epigastrium lymphadenopathy	Yes	Yes	CT scan of abdomen, PET scan	Lymph node biopsy, exploratory laparoscopy	Nodular lymphoma (stage IIIb)	1,567.06
Multiple enlarged lymph nodes in the pelvis	Yes	No	None	None	No finding	0.00
Meseneteric and retroperitoneal adenopathy	Yes	Yes	CT scan of abdomen and pelvis	None	Negative workup	814.04
Pelvic adenopathy	No		None	None	No finding	0.00
Pancreas						
Exophytic pancreatic mass	Yes	Yes	CT scan of pancreas, endoscopic ultrasound	None	Splenule	656.65
Mass in tail of pancreas	No	No	None	None	No finding	0.00
Gastrointestinal						
Soft tissue mass in distal esophagus	Yes	Yes	Endoscopy	None	No finding	144.62
Liver masses secondary to colon cancer	No	No	None	None	No finding	0.00
Vascular: abdominal aortic aneurysm (8 cm)	Yes	Yes	None	Abdominal aortic aneurysm repair	Large abdominal aortic aneurysm	0.00
Adrenal: left adrenal mass	Yes	Yes	MRI adrenals	None	Adrenal cyst	776.83
Other masses: retroperitoneal mass (2 × 3 cm)	Yes	Yes	2 CT scans of abdomen and pelvis, PET scan	None	Retroperitoneal mass	2,778.08
Total (39 findings)	35	32	24 CT scans (4 chest, 3 abdomen and pelvis, 13 abdomen, 2 chest, abdomen, and pelvis), 5 PET scans, 4 MRI scans, 10 ultrasounds, 1 endoscopy, 1 endoscopic ultrasound, 1 kidney, ureter, and bladder radiograph, 1 bronchoscopy	12 surgeries	5 Malignancies (lymphoma, recurrent lung cancer, 3 kidney malignancies)	25,268.00

ultrasound, one bronchoscopy, and one abdominal radiograph. These radiology and endoscopic studies generated a total radiology cost of $25,268 (Table 6).

The total cost of evaluating E3 ($87,911) and E4 ($25,268) lesions with radiology and endoscopy studies was calculated to be $113,179, based on an 86.5% follow-up rate. This resulted in a per-patient cost of $50 ($113 [179/2,277]). We extrapolated this cost for a 100% follow-up rate to be $130,842, or $57 per patient, for a complete radiology and endoscopic evaluation of an abnormal extracolonic finding on CTC.

There were a total of 19 surgeries performed to work up the patients in the E3 and E4 groups. Patients in the E4 group were significantly more likely to require diagnostic surgery to work up extracolonic findings than were patients in the E3 group (37.5% [12/32] vs 4.2% [7/167]; $p < 0.0001$). Of the 19 patients undergoing surgery, six extracolonic malignancies were identified. Interestingly, none of the eight patients (two in the E3 group and six in the E4 group) who underwent surgery for pelvic masses ultimately had a malignancy. Overall, only 0.83% (19/2,277) patients undergoing screening CTC required surgical evaluation as part of the workup.

A greater number of high-risk lesions (malignancy or dangerous aortic aneurysm) were identified in the patients who followed up their E4 findings (18.8% [6/32]) compared with E3 findings (0.6% [1/167]) patients ($p < 0.0001$). These data, along with surgery data, confirm the use of the CTC reporting and data system as an effective classification for organizing and triaging the workup of extracolonic findings. One patient in the E3 group had a stage IA adenocarcinoma of the lung and underwent curative resection. Six patients in the E4 group had five malignancies and one dangerous aortic aneurysm. The five malignancies included three renal cell carcinomas (two stage I and one stage II) cured by total nephrectomy, one recurrent bronchoalveolar carcinoma of the left lung (stage IV), and one nodular lymphoma (stage IIIb). The latter two patients underwent chemotherapy. One patient in the E4 group had an 8 cm abdominal aortic aneurysm that was repaired successfully. Four (66%) of six extracolonic cancers identified on CTC were cured with resection.

In this study population (n = 2,277), 8.52% (194/2,277) of patients were found to have a positive CTC (C3 or C4) that would require a follow-up colonoscopy for polypectomy. High-risk intracolonic findings included six colorectal adenocarcinomas and three adenomas with high-grade dysplasia. Of the nine patients, curative resection was accomplished in six patients (66%), whereas three of the CRCs had either lymph node involvement or distant metastasis. The size of these nine adenocarcinomas and high-grade dysplasia lesions ranged from 15 to 64 mm.

We examined the increase in diagnostic yield that results from considering both intracolonic and extracolonic high-risk findings identified on CTC. In this study, when we considered extracolonic findings, a total of 16 high-risk lesions (nine intracolonic and seven extracolonic) were identified, increasing the diagnostic yield by 78% (9–16; $p = 0.0156$) (Fig. 4). Of these patients, 69% (11/16) underwent curative resection (three colon cancers, three high-grade dysplasia colon lesions, three renal cell cancers, one pulmonary ad-

TABLE 6: Summary Table of All Patients With E3 and E4 Findings

Findings	No.	New	Follow-Up	CT	Ultrasound	PET	MRI	Other	Surgeries	Cancers	Approximate Radiology Costs ($US)
E3	211	195	167	158	47	5	9	14	7	1	87,911
E4	39	35	32	24	10	5	4	4	12	5	25,268
Total	250	230	199	182	57	10	13	18	19	6	113,179

Note—Except where noted, data are no. of patients.

enocarcinoma, and one aortic aneurysm), and 44.5% (5/11) of those patients had extracolonic findings on CTC.

Discussion

CRC screening is an accepted part of medical practice, with optical colonoscopy being performed every 10 years beginning at age 50 years. CTC has shown sensitivity and specificity similar to that of optical colonoscopy, as confirmed in a recent multicenter trial [13], with the added advantage of identifying extracolonic lesions. This study shows that significant extracolonic lesions identified during CTC increased the overall diagnostic yield of this examination. Specifically, clinically significant findings requiring urgent medical or surgical management increased by 78% (16 vs nine), resulting in the discovery of six more cancers and a large aortic aneurysm. Interestingly, CTC used for CRC screening identified almost as many extracolonic cancers as intracolonic cancers. There were a total of six extracolonic cancers (one lymphoma, three renal cell cancers, and two lung cancers) identified in this population, in addition to six colon cancers and three adenomas with high-grade dysplasia. Importantly, 66.7% (4/6) of these extracolonic malignancies underwent curative resection, compared with 50% (3/6) of colon cancers identified. Of 2,277 patients undergoing CTC for CRC screening, extracolonic findings doubled the yield of cancer identification from six to 12. This is a clear advantage of this new technology that needs to be weighed into future recommendations concerning CRC screening. Additionally, individuals interpreting CTC scans must be well trained in identifying both intracolonic and extracolonic lesions.

The negative aspects of extracolonic findings include the added diagnostic cost and physician time to evaluate these findings. Additionally, extracolonic findings may potentially subject patients to the increased anxiety and risks (e.g., biopsies and exploratory surgeries) associated with working up insignificant findings. The CTC reporting and data system was developed to accurately categorize extracolonic findings as significant or insignificant and to systematically identify lesions that required further evaluation. With the institution of the CTC reporting and data system, the actual number of patients requiring further evaluation decreased to primarily those with E3 and E4 findings (250 [11%] of 2,277 patients). The major benefit to this classification system is to provide the ordering physician confidence in avoiding unnecessary workup and cost of benign findings (i.e., those classified as E2). Hence, CRC screening with CTC and use of the CTC reporting and data system may have the added advantage of discovering curable extracolonic cancers for minimal additional cost.

In the current study, 89% of patients either did not have extracolonic findings (54%) or had insignificant E2 findings (35%) and required no further evaluation. The 11% of patients with significant extracolonic findings requiring follow-up in our study is similar to the 8–10% suggested by studies with asymptomatic screening populations [7, 8, 14, 15]. Of the 11% of patients with significant extracolonic findings, further evaluation was justified, because seven patients were identified with a high-risk lesion (malignancy or dangerous aortic aneurysm). The fact that almost all the high-risk lesions (6/7) were noted in patients with E4 findings shows the relative accuracy of the CTC reporting and data system when interpreted by radiologists trained and familiar with this categorizing system.

The radiology examinations used to evaluate these extracolonic findings increased the estimated cost of CRC screening with CTC by $57 per patient. This straightforward cost-effectiveness assessment examining short-term radiology costs has been duplicated in other studies with similar results [5, 8, 14, 16]. A more extensive cost-effectiveness analysis would include identifying every aspect of medical and clerical costs, which has been attempted by Gluecker et al. [8]. Including the additional costs of the surgeries, clinical visits, and other administrative costs would have added to the overall cost of working up extracolonic findings. Other studies dealing with screening populations have quoted slightly lower costs ($24–34) to work up these findings [5, 8, 14–16]. The difference in cost may be the result of increased Medicare reimbursement rates and our ability to capture the majority of radiology and procedural studies with our unified military medical databases. Another potential reason for increased workup costs could be related to variations in workup patterns at different institutions. Our institution may undergo a more extensive workup for a lesion that may be evaluated with a single study elsewhere. Another recent cost-effectiveness analysis created a Markov model to show that the addition of finding significant extracolonic findings during CTC made it more cost effective than colonoscopy [17].

There are limitations inherent to any retrospective study. For example, 100% follow-up is difficult to achieve in a retrospective cohort because it is not possible to control for patients' follow-up patterns. However, the military health care system is unique in that the electronic medical record spans the entire military worldwide, which means that we can follow up patients who have left our immediate area; such patients can be followed up anywhere in the military, which is the reason for our reasonably good follow-up rates (86.5%). It is possible that some patients are followed up in civilian care, and that is why we do not have their results included in our study. Other reasons that are important to mention are noncompliance or a decision by a provider not to pursue a workup, which may actually mean that our extrapolation to 100% follow-up rate may overestimate costs. This fact leads us to think that the additional cost would likely be somewhere between $50–57 per patient.

The retrospective design of this study allows us to understand the natural history of the outcomes of these extracolonic findings. The ability to follow these patients over time and note the natural radiology ordering patterns of primary care physicians is a realistic understanding of costs and studies generated. In addition, following patients out to their final diagnosis and, especially, establishing histologic diagnoses for these malignancies give us a better idea of the true rates of these malignancies. A recent meta-analysis by Xiong et al. [7] summarized

extracolonic findings in patients undergoing CTC. Seventeen studies were included in that analysis; however, it was made up of a heterogeneous population of both symptomatic and asymptomatic individuals. That study did not use the CTC reporting and data system to classify findings, and those authors reported an extracolonic malignancy rate of 2.7% (81/3,005) in their populations compared with the lower rate of 0.26% in our study [7]. There are multiple reasons for this high rate, including the heterogeneous populations studied and the fact the malignancy rates included "presumed malignancies." Most of these studies did not include biopsy-proven malignancy, which grossly overestimates the actual number of cancers. In our study, only five (16%) of 31 patients who were followed up for E4 findings suggestive of malignancy had a biopsy-proven malignancy. This finding suggests that a much smaller percentage of patients than is suspected after CTC will go on to have a true malignancy.

An important question regarding the cost of procedure is the potential morbidity of this extensive workup, which may require surgery to rule out these findings. In our population of 2,277 patients, 19 surgeries were performed to identify six malignant lesions and a high-risk aortic aneurysm. Interestingly, in patients with pelvic masses, none of the surgeries (0/8) proved to be a malignant ovarian mass, which was similar to findings (0/10) in a study by Pickhardt et al. [15] of a similar population of asymptomatic patients. In the bigger picture, only 0.8% (19/2,277) of patients required a diagnostic surgery, with 31.5% of these patients (6/19) with histologically proven malignancy, which seems to be an acceptable risk for a substantial gain. The overall morbidity and financial impact of extracolonic findings on a screening population seems minimal for relatively high reward.

Another strength of our study is the CTC technique and protocol used. CTC was performed using the technique previously described by Pickhardt et al. [3], which achieved sensitivities and specificities (> 90%) similar to those of optical colonoscopy in identifying colonic lesions larger than 8 mm. In our study, follow-up optical colonoscopy was recommended for 8.52% (194/2,277) of patients, which is similar to a referral rate of 7.9% in a screening population in a recent study by Kim et al. [4] that used similar colonic preparations and computer software. These similar follow-up rates attest to the consistency of CTC when using similar methodologies and interpretation by well-trained radiologists.

Between 1998 and 2008, there were 20 studies with populations of 40–3,120 patients that described CTC extracolonic findings in patients that were symptomatic or asymptomatic or both [3, 4, 6–8, 10, 11, 14–16, 18–27]. Of these 20 studies, seven enrolled more than 500 patients and five enrolled more than 1,000 patients; one study was a systematic review [3, 4, 7, 8, 14, 15, 18]. Studies that included symptomatic patients tended to identify more extracolonic cancers. Of the four studies (n > 1,000) of asymptomatic screening populations reporting data on both intracolonic and extracolonic cancers, there were a total of 25 (0.38%) extracolonic cancers and 22 (0.33%) CRCs among 6,583 patients [3, 4, 18]. When taking extracolonic malignancies into account, the diagnostic yield for identifying malignancies on screening CTC in these three large studies increased by 113%, from 22 to 47. In our study, we identified a similar rate of extracolonic malignancies (0.26% [6/2,277]) and intracolonic malignancies (0.26% [6/2,277]), which also doubles the yield (from six to 12) of identifying any malignancy.

It is important to understand that CTC is by no means a replacement for a CT of the abdomen and pelvis for detecting significant extracolonic lesions. Because of the lack of IV contrast material and the low dose of radiation, the sensitivity of CTC for identifying extracolonic lesions is much lower than that for a regular CT scan [9, 19]. This message needs to be communicated to referring physicians and patients undergoing CTC for screening. Although CTC can identify lesions outside of the colon, these findings often have to be further characterized, and this test should not be relied on as a tool to rule out disease in the abdomen or pelvis.

In conclusion, although the medical community has already accepted that CRC screening is cost effective and saves lives, CTC not only identifies CRC but also doubles the yield of identifying significant early extracolonic lesions, resulting in lives saved. These results represent a compelling reason to consider CTC either as an alternative to optical colonoscopy CRC screening or as a onetime procedure to identify significant treatable intracolonic and extracolonic lesions.

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